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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,592	08/17/2005	Ronald Rodriguez	58799(71699)	9269

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,592	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/24/07,7/18/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17,19,20,22 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17,19,20,22,33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

In view of the cancellation of claims directed to a non-elected invention, the election/restriction is moot.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/24/07 is being considered by the examiner.

Specification

The disclosure is objected to because of the following informalities: page 8 lines 26 and 27 are missing the filing date and Accession Number for cell referred to as DPL.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 19, 20, 22, and 33-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are readable on a genus of cell lines comprising a mutated EF-2, wherein the cell line is resistant to either DTA or PEA. The specification contemplates production of a mutated EF-2 gene that encodes an EF-2 protein that is mutated at codon 705. The instant specification and prior art provide sufficient description of some species of mutated EF-2 genes that make cell lines resistant to DTA or PEA (pages 7-8). However, the specification does not teach a structure/function correlation between each species. Neither the specification nor the prior art teach a genus of cells lines comprising a mutated EF-2 gene encoding a EF-2 protein that is mutated at codon 705 that must exhibit the desired biological activity. The genus reads on a mutated EF-2 gene from rat, mouse, dog, cat, etc. The specification teaches making a cell line comprising a human EF-2 gene encoding an EF-2 protein that is mutated at codon 705 (pages 12-13). In view of the lack of guidance in the specification and the prior art, the skilled artisan would have to further experiment (NOTE: undue experimentation is not being discussed here just further experimentation since undue experimentation is directed to an enablement rejection) to determine whether or not other EF-2 genes encoding an EF-2 protein mutated at codon 705 possess the desired biological activity. Therefore, in view of the lack of guidance for whether or not any other mutated EF-2 encoding an EF-2 protein that is mutated at codon 705 has the desired biological activity, the specification does not provide sufficient description of a genus of cell lines comprising a mutated EF-2 gene encoding an EF-2 protein that is mutated at codon 705. In view of the disclosure in the specification, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more

than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for a genus of cell lines comprising a mutated EF-2 gene encoding an EF-2 protein that is mutated at codon 705; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of a mutated EF-2 gene encoding an EF-2 protein that is mutated at codon 705 that must exhibit the disclosed biological functions as contemplated by the claims.

Teaching a mutated human EF-2 gene encoding an EF-2 protein that is mutated at codon 705, it is not sufficient to support the present claimed invention directed to a genus of cell lines comprising a mutated EF-2 gene encoding an EF-2 protein that is mutated at codon 705, if the claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of cell lines comprising a mutated EF-2 gene encoding an EF-2 protein that is mutated at codon 705 that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan

cannot envision the detailed structure of a genus of mutated EF-2 genes encoding an EF-2 proteins that are mutated at codon 705 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 16, 17, 19, 20, and 22 remain and claims 33-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing a cell in vivo using direct delivery of the adenovirus to the cell and a method of killing a cell in vitro, does not reasonably provide enablement for a method of killing a cell in vivo using a genus of administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention reads on a method of killing a cell that is sensitive to DT-A or PEA. The cell can be a cancer cell. The cell can be either in vitro or in vivo. The claimed invention embraces using a genus of administrations routes to a cell in vivo.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art

without undue experimentation (United States v. Technologies Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

The invention lies in the field of gene therapy.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art for gene therapy is exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several

major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, the state of the art of gene therapy is considered highly unpredictable.

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000) and McNeish et al (Gene Therapy 2004, Vol. 7, 1-7). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. None the less, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious

contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).

Vile further discusses:

A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).

Applicants provide no working examples of the claimed invention. Applicants do produce a packaging cell line for producing an adenovirus expressing A subunit of Diphtheria Toxin (DT-A) or Pseudomonas Exotoxin A (PEA). However, the relevance of this data to killing cells in vivo is unclear at best because neither the applicants nor the prior art provide a correlation or nexus between the results obtained by applicants with practicing the claimed gene therapy method. However, the prior art (Maxwell et al., Cancer Research, 1986, cited on PTO-1449) teaches that DT-A and PEA can be used to kill tumor cells in vivo. Thus, the skilled artisan would reasonably determine that the toxins could be used to kill cells sensitive to PEA or DT-A in a subject.

Furthermore, with respect to the claimed methods reading on a cell in vivo, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration and/or systemic administration of an adenovirus would result in a therapeutic response using a vector embraced in the claims. The applicants teach IJ or IP were suitable administration routes for delivering an adenovirus comprising the claimed nucleic acid into the liver of mice infected with HCV. The skilled artisan cannot reasonably extrapolate from the results using an adenovirus to a genus of vectors because each vector has a different mechanism and tropism. The state of the art for the route of administration for gene therapy as exemplified by Verma (supra) and Vile (supra), indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In view of the art of record, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to a genus of administration routes to generate a therapeutic response in a genus of subjects with HCV.

In conclusion, the instant specification and claims coupled with the art of record, at the time the invention, was made only provide enablement for an in vitro method of suppressing growth of a cancer cell and an in vivo method of suppressing growth of a cancer cell in a subject comprising direct administration to the cancer cell and not for the full scope of the claimed invention. Given that gene therapy wherein a genus of nucleic acids was employed to correct a disease or a medical condition in a genus of mammals was unpredictable at the time the

invention was made, and given the lack of sufficient guidance as to a gene therapy method for treating a genus of cancers in a genus of mammals, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 4/24/07 have been fully considered but they are not persuasive.

In response to applicant's argument that a genus of administration routes for use in the claimed invention is enabled (see specification), the argument is not found persuasive because the art of record teaches the problems of delivering an adenovirus to cells in vivo. The specification does not teach how to overcome these problems. For the reasons of record, the mere contemplation in the instant specification does not provide sufficient and/or factual evidence for practicing the claimed method without an undue amount of experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 35-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35-38 recite the limitation "the cells" in line 1. There is insufficient antecedent basis for this limitation in the claims. In view of the teaching in the specification it appears the limitation is directed to the packaging cell line. Suggest amending the limitation to -- the packaging cell line --.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16, 17, 19, 20, 22, and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez et al. (Proceedings of the American Association for Cancer Research 37, 346:2358, 1996) taken with Lieber et al. (US 6,686,196) and Fallaux et al. (US

5,994,128) in further view of Horlick et al. (US 6417002, AB). Rodriguez teaches that a nucleic acid encoding DT or PEA can be used in cancer gene therapy using an adenovirus. However, Rodriguez does not specifically teach the method steps for practicing a method of cancer gene therapy.

However, at the time the invention was made, Lieber et al. teach using an adenovirus (E1-) comprising a transgene, wherein the transgene can be either PEA gene or DT gene, in a method of treating tumor in a subject (columns 9, 10, and 21-28).

In addition, at the time the invention was made, Fallaux et al. teach a method of producing replication defective adenovirus using PER.C6 cells, wherein producing replication competent adenovirus is avoided (columns 43-46). See pages 8 and 9 of the instant specification. Also see MPEP 2129: ADMISSIONS BY APPLICANT CONSTITUTE PRIOR ART.

In addition, at the time the invention was made, Horlick el. al teach a method of producing cells resistant to PEA or DT, wherein the cells have a mutant elongation factor 2 gene (EF-2) (columns 7, 11, and 13).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Rodriguez taken with Lieber et al. and Fallaux et al. in further view of Horlick et al., namely to use PER.C6 cell line containing a mutant E2F gene to produce replication defective adenovirus (E1-) comprising PEA gene or DT-A gene in a method of killing tumor cells. One of ordinary skill in the art would have been motivated to combine the teaching to avoid killing the helper cell line for producing the

adenovirus. In addition, one of ordinary skill in the art would have been motivated to use PER.C6 to avoid the producing of replication competent adenovirus.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments with respect to claim 16, 17, 19 and 22 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764.

The examiner can normally be reached on Monday through Friday from 6:30 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, SPE – Art Unit 1635, can be reached at (571) 272-0763.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Brian Whiteman/
Primary Examiner, Art Unit 1635